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for dyspepsia. Age, gender, education, physical and mental health, pain, disability, and locus of control were not associated with MARI.
**Conclusions:** This study quantified osteoarthritis patients' preferences toward trade-offs between the risk of specific side effects of treatment and pain relief. As expected, the average additional risk that would be acceptable to subjects varied by side effect and increased in conjunction with the amount of potential pain relief. For all side effects, the acceptable level of risk for a given level of pain relief varied substantially among the subjects. Demographic, clinical, and psychological factors did not explain the variation in trade-off preferences. The study demonstrated the usefulness of the probabilistic threshold technique in eliciting preferences for trade-offs between the risk of side effects and pain relief. These observations are important for the development of practice guidelines for physicians and patients' decision aids that can foster individualized, evidence-based yet preference-sensitive care for patients with OA.

## I-10 INTRA-ARTICULAR THERAPIES FOR OA: TARGETS OF INTEREST FOR INTRA-ARTICULAR THERAPY AND STRATEGY TO PROMOTE INCREASED EFFICACY

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**Purpose:** No treatments capable of slowing the osteoarthritic process have been identified so far. Intra-articular treatment is a promising new approach that targets locally released cytokines and proinflammatory mediators in the synovial fluid. Furthermore, intra-articular treatment may be the best way to access the cartilage and synovial membrane and offers a better risk-benefit ratio than systemic treatment.
**Methods:** Large review of the literature concerning i.a therapies was performed excluding current intra-articular treatments which are available, namely, glucocorticoid injection, hyaluronic acid injection, and joint lavage.
**Results:** Targeted treatments designed to restore the balance between prodegradative cytokines and anabolic factors must be developed. Il-1 $\beta$ and TNF$\alpha$ are the most powerful cytokines in OA. Cytokine blockers can be injected intra-articularly, either directly or via gene therapy. Intra-articular injection of Il-1 receptor antagonist (Il-1-ra) produced promising results in animal models of OA. Il-1-ra injection is well tolerated in humans. However, in the only randomised controlled trial, a single Il-1-ra (50 or 150 mg) injection for knee osteoarthritis had little effect, possibly because of the short half-life of this cytokine antagonist. Intra-articular TNF$\alpha$ antagonist therapy has not been evaluated in clinical trials in humans. Downstream from Il-1$\beta$ and TNF$\alpha$, caspases can be blocked by direct injection of caspase inhibitors. Synovitis is thought to be involved in OA progression and therefore constitutes a major target. Depletion of synovial-membrane macrophages is associated with decreased metalloproteinase expression. Injection of an agent that blocks bone remodelling is an original and appealing approach. In mice, intra-articular injection of osteoprotegerin decreased the severity of OA lesions. Injection of anabolic factors might promote cartilage repair, thereby slowing the osteoarthritic process. Intra-articular injection of encapsulated bFGF microspheres holds some promise. TGFb is an extremely powerful stimulant of cartilage repair but also induces synovial membrane fibrosis and osteophyte growth. To avoid these adverse effects, gene therapy using both TGFb and Smad 7 has been used in experimental models of OA. The short half-lives of growth factors and cytokine antagonists indicates a need for developing new delivery strategies, such as liposomes, microspheres, and gene therapy, all of which exhibit limitations.
**Conclusions:** Intra-articular therapy holds promise for the treatment of OA, although many issues await resolution.

## I-11 FUNCTIONAL TISSUE ENGINEERING OF CARTILAGE

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**Purpose:** The purpose of cartilage functional tissue engineering is to produce a tissue whose mechanical properties allow it to sustain the physiological load magnitudes encountered in vivo. Based on our understanding of cartilage mechanics, these properties are critically dependent on the proteoglycan and collagen content of engineered cartilage, as well as the ultrastructural organization of the collagen matrix.
**Methods:** Recent in vitro tissue engineering studies of bovine chondrocyte-seeded agarose constructs have demonstrated that it is possible to produce native levels of proteoglycans (~6% w/w) in 4 to 8 weeks. These results are achieved by using a chemically defined chondrogenic culture medium with administration of TGF-$\beta$3 over the first two weeks. The resulting equilibrium compressive mechanical properties of the constructs match the values of native cartilage. However, collagen content levels (~4% w/w) remain below native levels (~15% w/w), and various strategies have been explored to further increase collagen synthesis. This lower collagen content is believed to be the primary reason that compressive properties of cartilage under dynamic loading remain below native levels.
**Results:** Under these conditions, animal studies have shown that tissue constructs show a variable ability to survive physiological loading conditions in vivo. Implanted small cylindrical constructs that are buttressed by healthy host cartilage show encouraging outcomes, whereas complete resurfacing of an articular layer with an anatomically shaped tissue construct fares more poorly.
**Conclusions:** These findings emphasize the need for functional tissue engineering that can reproduce the mechanical properties of native cartilage prior to in vivo implantation. The most critical need at this time is the necessity to increase collagen content to native levels, to improve the compressive properties of tissue constructs under dynamic loading. Some of our recent studies show that improvements in collagen synthesis may be achieved by delaying the relatively rapid accumulation of proteoglycans, using selective and timely enzymatic degradation.

## I-12 VALUE OF AUTOLOGOUS CELL TRANPLANTATION IN THE TREATMENT OF OSTEOARTHRITIS

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**Purpose:** Chondrocyte transplantation (ACT) has been a widely used clinical strategy in the repair of damaged cartilage from lesions resulting from traumatic injuries. In the last decade good clinical results have been obtained together with the formation of a new tissue with many hyaline features. More recently, suitable scaffolds loaded with chondrocytes have been used to hold the cells in the defect site, thus, permitting their proliferation, differentiation and maintenance of the chondrocyte phenotype. We explored the ACTapproach to treat osteoarthritis (OA) lesions by using an experimental animal model of OA into which autologous marrow-derived mesenchymal stem cells (MSCs) were seeded onto a hyaluronan-based scaffold (Hyaff®-11, Fidia Advanced Biopolymers, Abano Terme, PD, Italy) that was surgically positioned on the cartilages lesions of the knee.
**Methods:** Rabbit knee joints were bilaterally subjected to anterior cruciate ligament transection (ACLT) to surgically induce OA. Autologous rabbit MSCs have been isolated from the bone marrow, expanded in vitro and loaded on a hyaluronan polymeric scaffold (Hyaff®-11). After 8 weeks, necessary to the development of cartilage surface damage, animals were treated with MSCs seeded onto Hyaff®-11 scaffold in the left condyle and unseeded Hyaff®-11 in the controlateral knee. Untreated (sham operated) rabbits with ACTL were used as control. All the animals were sacrificed at 3 and 6 months after surgery. Morphological, histological, histomorphometric and immunohistological evaluations were performed.
**Results:** OA changes developed in all animals subjected to ACLT. The predominant macroscopically observed OA changes were mild (lateral femoral condyle) or moderate (medial femoral condyle) ulcerations. Articular cartilages harvested after 8 weeks from ACLT and stained with Safranin-O clearly showed a superficial fibrillation with microscopic cracks and proteoglycan depletion in the cartilage matrix particularly in the medial condyle. At 3 and 6 months the untreated cartilage presented the progression of OA process with evident signs of matrix loss extended to deep zones of cartilage and particular evident in the medial condyle. The animals treated with MSCs-HA scaffolds showed a better matrix organization, a higher presence of proteoglycan component and normal distribution of the cells together with an increase in collagen II expression in comparison with rabbits treated with HA scaffold alone or the untreated groups. In the animals treated with MSCs-HA scaffolds histomorfometric parameters showed a decrease of modified Mankin score after 3 and 6 months after the treatment.
**Conclusions:** The present study demonstrates that the use of MSCs loaded on a HA scaffold can contribute to the regeneration of a new cartilage tissue in a rabbit model of OA. It is possible to speculate that the beneficial effects of MSCs might reflect, in part, some trophic and protective activities they exert on injuried cells and tissue, togheter with their property to differentiate into chondrocytic lineage.